3. Seibert, F. B., and Watson, D. W.: J. Biol. Chem., 140:55, 1941.

4. Dische, Z.: Microchemie, 8:4, 1931. Seibert, F. B.: J. Biol. Chem., 30:2226, 1936.

5. Hewitt, L. F.: Biochem. J., 30:2226, 1936. Kekwick, R. A.: *Ibid.*, 32:552, 1938. Blix, G., Tiselius, A., and Svensson, H., J. Biol. Chem., 137:485, 1941.

BIOTIN IMMUNITY IN PROTOZOAN INFECTIONS

It has long been known that famine is frequently accompanied by severe epidemics of malaria, from which it has been deduced[1] that malnutrition lowers normal resistance to pathogenic protozoa. Experimental evidence, however, has contradicted this deduction. Passmore and Sommerville,[2] for example, found that monkeys maintained on a famine diet did not develop severer infections with *Plasmodium cynomolgi* than did adequately fed controls. That there is an element of truth in the prevalent belief, however, is currently reported by Trager[3] of the Rockefeller Institute, and by Caldwell and György[4] of Western Reserve University, who have studied the effects of biotin deficiency and biotin therapy on malaria and trypanosome infections in laboratory animals.

Du Vigneaud[5] of Cornell University had previously alleged a correlation between the biotin titer of the blood of fowls and the severity of avian malaria infection. Applying this finding, Trager produced biotin deficiency in chickens and ducks by feeding them adequate diets plus a large amount of dried egg white. (The avidin of the egg white functions as an antibiotin.) Control animals were fed the same diet plus an equivalent amount of casein. Ducks on the egg-white diet began to show signs of biotin deficiency in two to four months. At or before this time the animals, together with an equal number of casein-fed controls, were inoculated intravenously with the same dose per unit of body weight of the blood of a malaria-infected donor.

As a typical experiment, five ducks that had been fed for fourteen days on the egg-white diet together with five casein-fed controls were each inoculated intravenously with the blood of the same malarial donor. After a lag phase of about forty-eight hours, the plasmodium count increased logarithmically in the blood of each animal. In the control ducks the average count reached 40 plasmodia per 100 r. b. c. by the fifth day. In the biotin-deficient ducks the count was 90 plasmodia per 100 r. b. c. on the same day. This is a 100 per cent increase in the severity of the infection in the malnutrition group. There was even a greater difference in the relative mortality of the two groups; only one of the casein-fed controls died on the sixth day, while there were four deaths in the biotin-deficient group. Similar differences were noted in chickens.

In both chickens and ducks the increased severity in the malnutrition group was proportional to the degree of biotin deficiency. This finding was confirmed by therapeutic tests, intraperitoneal injections of biotin concentrate into the deficiency animals, restoring their normal antimalaria resistance. Similar injections in animals fed adequate diets, however, had no demonstrable antimalarial effect, presumably due to rapid destruction in elimination of excess biotin.

Almost identical results are reported by the Western Reserve pediatricians, who studied the effects of a biotin deficiency in trypanosome infections. Several groups of rats were maintained on a modified egg-white diet, with controls reared on their routine stock diet. In a typical experiment, ten rats showing a fairly advanced stage of biotin deficiency together with thirteen adequately fed controls were each inoculated intraperitoneally with the same number of *Trypanosoma lewisi*. The resultant infections lasted from 7 to 28 days in the control group, an average of 16.9 days. In the biotin deficiency group the infection lasted from 14 to 49 days, an average of 34.9 days. Similar, though less pronounced, prolongations of the infection were noted in rats showing moderate or slight degree of biotin deficiency and even in those with a latent deficiency. Prolongation of the trypanosome infection could also be prevented in rats by daily subcutaneous injections of biotin concentrate during the course of the experimental infection.

Among the significant phenomena reported by Trager is his finding that the biotin level of the circulating blood of normally fed fowls increases rapidly during the early stages of experimental malarial infections, a phenomenon originally reported by certain Asiatic clinicians.[2] As soon as the biotin blood titer had reached its maximum, the plasmodia cease to multiply. Trager believes the increase in humoral biotin titer is due to a biotin release from the liver or from other storage tissues. Synthesis of biotin by the invading protozoan parasites, however, has not yet been ruled out.[4] Hyperbiotinemia is pictured by both investigators as an immunity mechanism. The excess biotin presumably inhibits protozoan infections either by its direct toxic action on the parasites,[3] or by activating antibodies or defensive enzymes.[4]

While the suggested theory of biotin immunity is controversial, it does furnish an ephemeral working hypothesis of major theoretical and clinical interest.

P. O. Box 51.

W. H. MANWARING,
Stanford University.

REFERENCES

1. Williams, C. D.: Lancet, 1:441, 1940.

2. Passmore, R., and Sommerville, T.: Jour. Malaria Inst. India, 3:447, 1940.

3. Trager, W.: Science, 97:206; Jour. Exp. Med., 77: 557, 1943.

4. Caldwell, F. E., and György, P.: Proc. Soc. Exp. Biol. and Med., 53:116 (June), 1943.

5. Du Vigneaud, V.: Science, 96:455, 1942.

Minorities are rich assets of democracy, assets which no totalitarian government can afford. For the majority itself is stimulated by the existence of minority groups. The human mind requires contrary expressions against which to test itself.—Wendell L. Willkie.